Epilepsy & Behavior 15 (2009) 98–105

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Large differences in blood measures, tissue weights, and focal areas of damage 1 year after postseizure treatment with acepromazine or ketamine

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ARTICLE INFO

Article history:
Received 1 November 2008
Revised 23 February 2009
Accepted 26 February 2009
Available online 1 March 2009

Keywords:
Lithium/pilocarpine seizures
Ketamine
Acepromazine
Rat
Thalamus
Hippocampal formation
Thyroid function
Alanine aminotransferase
Aspartate aminotransferase

ABSTRACT

Approximately 1 year after rats were seized as young adults with lithium (3 mEq/kg) and pilocarpine (30 mg/kg) and given acepromazine or ketamine, 18 blood measures, wet tissue weights, and detailed damage scores for 107 brain structures were completed. Compared with normal and ketamine-treated rats, acepromazine-treated seized rats (total $n = 54$) had lighter pancreata and spleens and elevated aspartate aminotransferase and alanine aminotransferase blood levels. Even though average damage did not differ, the mosaic of brain damage completely discriminated the two seized groups. Differential effects of postseizure treatment on functions of the thyroid, pancreas, and spleen were indicated. Ketamine-treated seized rats were healthier than acepromazine-treated seized rats or normal rats. This experiment demonstrates the importance of whole-organism assessment and that the single administration of a specific drug after onset of status epilepticus can produce marked differences in the evolution of brain damage and its influence on specific organs for the rest of the animal's life.

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1. Introduction

The induction of epileptic seizures by a single therapeutic dosage of lithium (3 mEq/kg) followed 4 to 24 hours later by the cholinergic agent pilocarpine (30 mg/kg) produces status epilepticus (SE) within about 30 minutes [1,2]. The multifocal brain damage [3–6] that occurs within the rat brain during the subsequent several hours within primarily the entorhinal region, thalamus, subcortical telencephalon, substantia nigra, and cerebral cortices exhibits distinguishable patterns with specific temporal sequences that reflect the glucose utilization [7,8] and excessive activity [9] of specific subset sets of neurons within approximately 100 Paxinos and Watson [10]-defined regions.

It is well known that seizure latency [11,12] can be affected by different a priori neurochemical interventions [13,14]. However, specific classes of pharmacological treatments [15–17] following the onset of SE strongly affect the type and severity of neuronal damage. Different postseizure drug treatments, administered only once, also determine the specific mosaic of the differential necrosis within the affected areas.

The concept of the neuromatrix [18] predicts that different patterns of partial damage and the subsequent differential reorganization of synaptic networks should produce different effects on behavior. A single postseizure injection of 100 mg/kg ketamine normalizes rats' learning within a variety of contexts [19–21] compared with that of rats seized but given acepromazine to facilitate survival. Whereas spontaneous seizures emerge [22] after a "silent period" corresponding to the latency of neurogenesis within the dentate gyrus [23] in seized rats treated with acepromazine, such seizures are not observed in ketamine-treated rats [24,25].

The present experiments were designed to compare the "permanent" effects of a *single* postseizure injection of either ketamine (100 mg/kg) or acepromazine (25 mg/kg) following the onset of lithium/pilocarpine-induced seizures. We measured the concentrations of 18 blood constituents often employed for medical diagnosis, wet organ weights, and patterns of brain damage about *1 year* after seizure induction. In light of the reciprocal disruptions in pancreatic islet beta cell function and granule cell function in

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doi:10.1016/j.yebeh.2009.02.043

the hippocampus when one is lesioned [26] and the effects of cortical lesions on spleen and thymus weights [27], such inclusive analyses were considered appropriate.

We reasoned that although the brain is central to epilepsy, the effects on the entire body and blood chemistry are also important and may reveal insights into the complex dynamics of the whole organism. Our first general hypothesis was that if structure dictates function, alterations in the pattern of neuronal dropout resulting from postseizure treatment with one of two different drugs (ketamine or acepromazine) should result in different changes in blood chemistry and organ weights that should be evident 1 year later. Our second general hypothesis was that the organism can be viewed as a complex of chemical matrices. Consequently, tissues that share similar chemistry, such as the zinc-related enzymes, common within the pancreas and the dentate gyrus of the hippocampal formation, should be quantitatively associated.

2. Procedure

2.1. Subjects

A total of 54 male Wistar albino rats, approximately 80 to 90 days of age at the beginning of the study, were selected as subjects. They had been obtained about 3 to 5 weeks earlier from Charles River Breeders, Quebec, QC, Canada. Half of the rats were maintained in standard metal (wire) cages (40.5 × 25 × 18 cm deep); the remaining rats were maintained in plastic shoebox cages (46 × 20 × 14 cm) containing spruce wood shavings that were changed twice per week.

Food (Purina Rat Chow) and water were available ad libitum. The light:dark cycle was 12:12 with photophase onset at 0800 hours local time; the ambient temperature was maintained between 20 and 21 °C. All procedures were approved by the local Animal Care Committee and were in compliance with the Canadian Council on Animal Care guidelines.

2.2. Seizure induction and treatment

After about 3 to 5 weeks of habituation to the colony conditions, 38 of the rats were injected subcutaneously in the left flank with 3 mEq/kg lithium chloride (3 mEq/cc), followed 4 hours later by a single systemic injection (right flank) of 30 mg/kg pilocarpine (30 mg/cc). The other 18 rats remained as nonseized controls. About 8 rats were injected at any given time and placed in their own compartments (modified small plastic cages) in the observation room. Following injection of pilocarpine, the rats were closely monitored for the onset of 4/5 motor seizures [28], and the time or latency (in seconds) to the onset of the seizure (SE) was recorded.

Within 5 minutes of the first overt behavioral signs of SE, 16 rats received a single injection of ketamine (Sigma, St. Louis, MO, USA), whereas another 22 rats received 25 mg/kg acepromazine (Ayerst Laboratories, Montreal, QC, Canada). Within any given block of experiments half the rats were injected with acepromazine and the other half were injected with ketamine. We did not include non-status epilepticus control groups, that is, groups that received either acepromazine or ketamine but not lithium/pilocarpine, because there is no evidence that acute ketamine or acepromazine produces any acute effects on brain morphology, especially 1 year after the injection.

Because we knew from previous experiments that lithium/pilocarpine-induced seizures without treatment result in 95% mortality [2,3], we did not include this procedure. Our primary interest was to investigate the long-term differences between the two postseizure drugs. We did not include drug-only (single injection of either ketamine or acepromazine) groups in normal rats because we had no evidence from either our casual observations or the known effects of these drugs that this singular event would produce changes evident 1 year later in either tissue weights or blood chemistry.

2.3. Measures

Following seizure induction, the rats were maintained in groups of one or two per plastic or wire cage. After approximately 11 months (M = 342, SEM = 25 days) had elapsed, the rats were taken from their cages, weighed, and then quickly decapitated within 20 s. Over a 6-month period involving nine blocks (six rats per block), trunk blood was collected and serum was obtained and stored at 4 °C before it was analyzed. The brain was removed within 5 minutes, weighed, and fixed in ethanol–formalin–acetic acid [29]. Within the subsequent 30 minutes, the following organs were removed and weighed on an analytical balance: thyroids, thymuses, spleens, adrenals, testicles, pancreases, and pituitaries.

The blood was analyzed automatically by the experimenters at a local hospital's clinical laboratory for aspartate aminotransferase (previously serum glutamic–oxalacetic transaminase), glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, phosphorus, lactic dehydrogenase, creatine phosphokinase, alkaline phosphatase, alanine aminotransferase (previously serum glutamic–pyruvic transaminase), uric acid, triglycerides, cholesterol, thyroid-stimulating hormone, and free thyroxine. There were a total of six separate runs over a 6-month period with nearly equal numbers of control, seized + acepromazine, and seized + ketamine rats per run. One sample was lost during the analyses.

Twelve cerebrums from the acepromazine-treated group and 14 cerebrums from the ketamine-treated group were processed, embedded in paraffin, and sectioned at 10 μm. Every tenth slide was stained with toluidine blue O between the level of the posterior and anterior commissures. Each structure at each level as designated by Paxinos and Watson [10] was ranked in increments of 10% for proportion of neuronal dropout compared with that structure from a normal age-matched brain as described previously [22]. This ranking from 0 to 100% was averaged for all sections containing a structure. For first-order comparisons, the average damage scores for all individual structures within the thalamus, entorhinal-pyriform area (“limbic cortices”), neocortices, basal ganglia, hippocampal formation, amygdala, and substantia nigra were obtained.

When compared with the actual neuronal count for 10 structures reported by Peredery et al. [5], the correlation between the ordinal rating and actual cell counts, even though this involved two different studies and different brains, was 0.70. We [30] have found that the damage effects within specific structures for these dosages of lithium and pilocarpine are so similar to those for 300 mg/kg pilocarpine [31] across studies by different experimenters that meaningful and revealing correlations have been found between diverse measures even though different rats were compared.

Thyroids from 12 rats (4 control, 4 seized + ketamine, 4 seized + acepromazine) that had been fixed in ethanol–formalin–acetic acid were selected from the main pool. They were processed, embedded in paraffin, and sectioned at 6 μm. Two sections from each thyroid were stained with hematoxylin and eosin for follicular detail [32] and two sections were stained with toluidine blue O for mast cells [33]. The numbers of follicles per section were counted for each rat.

2.4. Statistical analyses

One-way analyses of variance were completed for all blood and tissue measures for the three groups. The post hoc analysis was

Tukey's set at $P < 0.05$. Two-way analyses of variance and Kruskal–Wallis tests (nonparametric group comparisons) were completed where appropriate between the two seized groups for all the measures of brain damage. Because of the number of structures involved, $P < .001$ was set for criteria; ω'^2 estimates were calculated to show effect size. It is defined as the amount of variance in the dependent measure accommodated by the treatments.

Spearman ρ correlations were completed to minimize the potential contributions from outliers and distorted distributions. Stepwise discriminant analyses were used to classify the two seized groups on the basis of their postseizure drug treatment. To discern the effects of the potential interactions between treatments (control, seized + ketamine, seized + acepromazine) and type of housing (wire vs plastic cage) on the measures, considering the long duration of maintenance of the rats, two-way analyses of variance were employed. All analyses involved SPSS software on a VAX 4000 computer.

3. Results

3.1. Blood measures

The means and SEM for the blood measures that displayed statistically significant differences between the three groups (seized + acepromazine, seized + ketamine, and nonseized controls) are listed in Table 1. The only statistically significant group differences (all $df = 2, 50$) were found for levels of aspartate aminotransferase (AST) ($F = 3.89$, $P < 0.05$) and alanine aminotransferase (ALT) ($F = 3.61$, $P < 0.05$). Post hoc analyses indicated that seized rats treated with acepromazine had significantly elevated levels of AST and ALT compared with seized rats treated with ketamine or controls. The group differences for levels of blood sodium approached statistical significance. ($F = 2.45$, $P < 0.10$). The means and SEM for all blood measures are given later in Table 8 in which the values for rats housed in plastic shoebox cages are compared with those housed in conventional wire cages.

3.2. Tissue weights

The means and SEM for the tissues that displayed significant group differences (all $df = 2, 50$) are also listed in Table 1. The postseizure ketamine-treated group had significantly heavier body weights ($F = 7.37$, $P < 0.01$) and thymuses ($F = 4.25$, $P < 0.05$, $\omega'^2 = 13\%$) compared with the nonseized controls and acepromazine-treated group, which did not differ significantly from each other. The postseizure acepromazine-treated group had lighter spleens and pancreases compared with the controls. There were no statistically significant group differences for the other tissues. The grand means (SD) for all 54 rats were: brain 2.20 (0.14) g, thyroids 38.9 (18) mg, adrenals 71.7 (26.2) mg, gonads 3.74 (0.76) g, and hypophyses 18.7 (8 mg).

3.3. Proportions of neuronal dropout in large areas

The means and SEM for the proportions of damage (neuronal dropout) within the major regions that were most affected following the induction of lithium/pilocarpine seizures for the two groups (total $n = 26$) are listed in Table 2. Although the mean proportion of total damage for all structures did not differ significantly between the two groups of seized rats, univariate tests indicated that the ketamine-treated rats displayed more damage in the limbic areas ($F = 18.90$, 45% of variance), whereas the acepromazine-treated rats showed more damage in the thalamus.

The variability of damage within the limbic cortices and thalamus was significantly greater for the group that displayed the higher means for these areas. However, nonparametric analyses (Kruskal–Wallis) demonstrated the group differences were not due to outliers. The correlations (Spearman ρ) between average scores for the average damage for all brain areas and age ($\rho = 0.13$), time since seizure induction ($\rho = 0.16$), and age at time of seizure ($\rho = -0.28$) were not statistically significant.

Discriminant analysis (standardized canonical discriminant function coefficients in parentheses) indicated that the combination of damage within the limbic cortices (−0.95), thalamus (0.75), and basal ganglia (0.42) resulted in accurate classification of 25 of the 26 (96%) rats within their conditions. The canonical correlation coefficient was 0.82 ($\chi^2(4) = 24.99$, $P < 0.001$) and explained 69% of the variance.

3.4. Correlations between blood measures and major areas of damage

Spearman ρ correlations between the three general areas (limbic area, hippocampus, thalamus) that showed the largest numbers of criterion correlations between the proportion of damage and blood measures are listed in Table 3 for the seized rats that were given either acepromazine or ketamine. The most conspicuous correlation was the strong *negative* correlation between thyroid-stimulating hormone and damage within the thalamus for acepromazine-treated rats, but the *positive* correlation between thyroid-stimulating hormone and thalamic damage for the ketamine-treated rats.

Damage within these areas for acepromazine-treated rats was associated with altered levels of electrolytes and creatine phosphokinase, whereas damage within the ketamine-treated rats was more associated with altered levels of albumin and ALT. Only the rats treated with acepromazine displayed statistically significant correlations between time since seizure induction and blood measures. These values were AST (−0.62), sodium (0.76), calcium (0.56), lactic dehydrogenase (−0.81), uric acid (0.75), triglycerides

Table 1
Means and SEMs for statistically significant differences in blood measures and wet tissue weights between the three groups.

Measure	Controls ($n = 16$)		Seized + acepromazine ($n = 22$)		Seized + ketamine ($n = 16$)	
	M	SD	*M*	SD	*M*	SD
AST	128.9[a]	14.4	199.0[b]	21.3	165.711	12.2
Na	156.1	1.2	153.4	0.6	154.1	0.8
ALT	72.6[a]	8.6	109.7[b]	12.1	82.1[a]	7.6
Body weight (g)	683.4[a]	26.9	628.3[a]	22.4	763.5[b]	26.2
Thymus weight (g)	93.6[a]	9.5	99.8[a]	13.5	160.5[b]	24.9
Spleen weight (g)	1.8[a]	0.1	1.3[b]	0.1	1.6	0.1
Pancreas weight (g)	1.4[a]	0.1	1.1[b]	0.1	1.2	0.1

[a,b] a versus b = $P < 0.05$.

Table 2
Means and SEM for the proportion of damage within various brain regions of rats seized with lithium/pilocarpine and treated with either acepromazine or ketamine.

Measure	Acepromazine		Ketamine	
	M	SD	*M*	SD
All damage	21.4	8.0	18.5	5.4
Neocortices	17.0	10.9	19.0	20.7
Limbic cortices	14.1[a]	6.2	44.0[b]	22.9
Basal ganglia	8.9	5.0	7.2	3.3
Hippocampal formation	12.3	3.0	6.2	5.8
Amygdala	24.1	8.2	29.7	8.9
Thalamus	24.7[a]	11.8	14.1[b]	4.1
Substantia nigra	21.9	10.8	15.0	8.9

[a,b] $P < 0.05$.

Table 3
Spearman (ρ) correlations between proportion of damage within the major regions and blood measures for rats seized and treated with acepromazine ($n = 12$) or ketamine ($n = 14$).

Measure	Limbic areas		Hippocampus		Thalamus	
	Ace	Ket	Ace	Ket	Ace	Ket
Blood						
Sodium	0.69[a]	−0.24	0.74[a]	−0.08	0.49	−0.33
Calcium	0.56[a]	0.00	0.44	0.26	0.41	−0.67[a]
CPK[b]	0.57[a]	−0.16	0.67[a]	0.01	0.45	−0.26
Triglycerides	0.55[a]	0.30	0.44	0.10	0.45	0.01
TSH	−0.39	0.13	−0.64[a]	−0.32	−0.73[a]	0.77[a]
ALT	−0.06	0.06	−0.13	0.79[a]	0.18	0.05
Albumin	0.00	−0.75[a]	−0.11	−0.20	−0.20	0.16
Tissue						
Thyroid	−0.01	0.03	−0.23	−0.28	−0.57[a]	−0.09
Thymus	−0.52[a]	−0.25	−0.46	0.16	−0.55[a]	−0.41

[a] $P < 0.05$.
[b] CPK, creatine phosphokinase; TSH, thyroid stimulating hormone.

(0.86), cholesterol (0.80), albumin (−0.74), and free thyroxine (−0.75).

3.5. Differences in ketamine versus acepromazine treatment for individual structures

The means and SEM for all structures where group differences were $P < 0.01$ and more than 25% of the variance in histological score was accommodated by the treatment with ketamine vs acepromazine are listed in Table 4. The differential direction of proportion of damage is clear. For example, the ketamine-treated rats showed significantly more damage in the amygdalopiriform transition area (APIR)[1], whereas the acepromazine-treated rats showed more damage within the thalamic paratenial nucleus.

To discern which specific structures differentiated the two seized groups, discriminant analyses was completed for all structures assigned damage scores. The maximum number of steps was set at 5 to prevent spurious inclusions into the function by the stepwise procedures. The structures in which damage discriminated the acepromazine-treated from the ketamine-treated group with 100% accuracy were (standardized canonical discriminant function coefficients in parentheses): APIR (1.70), LPLR (−1.24) BLV (−1.16), PRS (0.70), and MGV (0.66). The significant [$\chi^2(5) = 40.57$, $P < 0.001$] canonical correlation coefficient was 0.92 (85% of variance explained).

Table 4
Means and SEM for the structures that displayed $p < 0.01$ significant differences in proportion of damage between seized rats administered acepromazine or ketamine after seizure onset.

Structure	Acepromazine		Ketamine		ω^2 (%)
	M	SEM	*M*	SEM	
PRH[a]	8	5	19	3	27
DEN	13	3	48	8	39
PIR	21	6	66	11	32
APIR	7	3	67	11	51
AAD	25	3	13	3	27
MEPV	24	4	9	2	34
BLP	12	3	39	7	31
BMP	20	3	58	8	41
PT	53	10	17	5	32
MDc	36	8	11	2	31
MDM	43	9	10	4	36
CM	20	4	35	2	34
Re	51	9	17	1	39
PF	34	4	49	3	27
LDVL	55	10	8	2	48
LDDM	38	8	5	2	43
LPLR	57	10	10	3	48
LPMR	40	9	10	3	34
LPLC	46	9	9	2	42
LPMC	45	8	9	2	4

[a] See footnote 1 for list of abbreviations.

For comparison the means and standard deviations for the centroids of the two groups were −2.45 (0.8) and 2.10 (0.9), respectively. The binomial multiple regression equation [$F(5,25) = 22.40$, $P < 0.001$), including the partial raw slopes (regression coefficients) with 1 = acepromazine and 2 = ketamine as the dependent variable, was $(0.01 \times \text{APIR}) - (0.009 \times \text{LPLR}) - (0.007 \times \text{BLV}) + (0.051 \times \text{PRS}) + (0.03 \times \text{MGV}) + 1.40$ (constant). The means and SEM for these structures for the acepromazine and ketamine groups, respectively, were: APIR 7 (3) and 67 (11), LPR 56 (10) and 10 (3), BVL 17 (5) and 46 (11), PRS 2 (0.7) and 4 (0.7), and MGV 4 (1) and 1 (0.7).

3.6. Correlations between blood measures, organ weights, and individual brain nuclei

The strongest Spearman ρ correlations ($P < 0.001$, to minimize spurious inclusions) between damage within individual structures and blood chemistry are listed in Table 5 for the acepromazine-treated rats and in Table 6 for the ketamine-treated rats. The range of damage for each structure is indicated as well. For thyroid-related correlations, the acepromazine-treated rats showed less thyroxine and TSH with more damage in the basolateral (ventral) amygdaloid nucleus, inner blade of the dentate gyrus, entorhinal cortices, and medial geniculate (primary and medial). On the other hand, the ketamine-treated rats showed elevated thyroxine levels with more damage in the centromedial nucleus and lateral dorsal thalamic nucleus.

All of the statistically significant correlations ($P < 0.01$) between wet organ weights and blood measures were for thyroid and pancreas only. Thyroid weights were correlated significantly (Spearman ρ in parentheses) with body weight (0.46), glucose (0.58), calcium (0.50), uric acid (0.62), triglycerides (0.70), cholesterol (0.79), and T4 (−0.73). For pancreas weights the significant correlations were with glucose (0.43), uric acid (0.45), and cholesterol (0.43).

[1] *Abbreviations used:* AAD, anterior amygdaloid area, dorsal part; AHIPM, amygdalohippocampal area, posteromedial part; APIR, amygdalopiriform transition area; ASTR, amygdalostriatal transition area; BLP, basolateral amygdaloid nucleus, posterior part; BLV, basolateral amygdaloid nucleus, ventral part; BMA, basomedial amygdaloid nucleus, anterior part; BMP, basomedial amygdaloid nucleus, posterior part; CA1 to CA4, hippocampal fields; CL, clastrum; CM, central medial thalamic nucleus; CPU, caudate putamen; CXA, cortex–amygdala transition zone; Den, dorsoendopiriform nucleus; DG, dentate gyrus; DLG, dorsal lateral geniculate nucleus; DSC, lamina dissecans of the entorhinal cortex; ENT, entorhinal cortex; EP, entopeduncular nucleus; FStr, fundus striati; GP, globus pallidus; Gu, gustatory thalamic nucleus; IAM, interanteromedial thalamic nucleus; IBL, inner blade of the dentate gyrus; LADL, lateral amygdaloid nucleus, dorsolateral part; LAVM, lateral amygdaloid nucleus, ventromedial part; LAVL, lateral amygdaloid nucleus, ventrolateral part; LHBL, lateral habenular nucleus, lateral part; LHBM, lateral habenular nucleus, medial part; LDDM, laterodorsal thalamic nucleus, dorsomedial part; LDVL, laterodorsal thalamic nucleus, dorsoventral part; LPLC, lateral posterior thalamic nucleus, laterocaudal part; LPLR, lateral posterior thalamic nucleus, laterorostral part; LPMC, lateral posterior thalamic nucleus, mediocaudal part; LPMR, lateral posterior thalamic nucleus, mediorostral part; MD, mediodorsal thalamus; MDC, mediodorsal thalamic nucleus, central part; MDM, mediodorsal thalamic nucleus, medial part; MEPV, medial amygdaloid nucleus, posteroventral part; MG, medial geniculate; MGM, medial geniculate medial part; MGV, medial geniculate ventral part; Pf, parafascicular thalamic nucleus; PIR, piriform cortex; PLCO, posterolateral cortical amygdaloid nucleus; PRH, perirhinal cortex; PRS, presubiculum; PT, paratenial thalamic nucleus; PVP, paraventricular thalamic nucleus, posterior part; Re, reuniens thalamic nucleus; SG, supragenicular thalamic nucleus; SNc, substantia nigra compacta; SNl, substantia nigra, lateral part; SunG, subgeniculate nucleus; VLG, ventral lateral geniculate nucleus; VPM, ventral posteromedial thalamic nucleus.

3.7. Correlations between damage in individual nuclei and wet tissue weights

The wet weights of tissues with which there were the strongest correlations ($p < 0.001$) with proportion of damage within any of the individual structures are listed in Table 7. The most frequent tissues whose weights were correlated with the proportion of damage were the thyroid and thymus for acepromazine-treated rats and the brain and the thyroid for ketamine-treated rats.

3.8. Thyroid morphology and correlations

There was a weak statistically significant difference between the number of follicles per total section of thyroid for the control ($M = 418$, SEM = 37), seized + acepromazine ($M = 480$, SEM = 55), and seized + ketamine ($M = 364$, SEM = 15) groups. Post hoc analysis indicated that the acepromazine-treated group had more follicles than did the ketamine-treated group. For all 12 rats there was a positive correlation ($\rho = 0.73$) between numbers of follicles and levels of AST. The numbers of mast cells within the perifollicular regions of the thyroid were correlated significantly with body weight ($\rho = -0.57$), blood phosphorus levels ($\rho = 0.57$), and free T4 ($\rho = 0.55$).

Table 5
Criterion correlations (Spearman ρ) between proportion of damage in various brain structures and blood measures for rats that were seized and injected with acepromazine about 1 year previously.

Structure		Blood measure	ρ
PRH[a]	2–16	Blood urea nitrogen	−0.76
PLCO	15–54	Sodium	0.82
BMA	10–70	Sodium	0.70
CXA	13–70	ALT	−0.78
BLV	00–50	Alkaline phosphatase	−0.89
BLV		Free thyroxine	−0.70
GP	00–22	Creatinine	−0.72
IBL	00–99	Sodium	0.87
IBL		Lactic dehydrogenase	−0.72
IBL		Triglycerides	0.72
IBL		Cholesterol	0.72
IBL		Free thyroxine	−0.79
DG	00–30	Uric acid	0.67
CA1	00–82	Sodium	0.75
CA2	00–30	Creatine phosphokinase	0.74
CA3	00–20	Lactic dehydrogenase	−0.78
CA3		Creatine phosphokinase	0.82
LHBL	10–50	Glucose	−0.70
LHBL		Lactic dehydrogenase	0.71
PVP	10–53	AST	0.70
PVP	10–53	Albumin	0.86
FSTR	00–30	Lactic dehydrogenase	−0.77
FSTR		Albumin	−0.66
ENT	00–25	Thyroid-stimulating hormone	−0.68
MD	00–90	Thyroid-stimulating hormone	−0.79
MDM	00–90	Thyroid-stimulating hormone	−0.73
LPLC	10–99	Blood urea nitrogen	−0.79
LPMC		Blood urea nitrogen	−0.83
MG	00–10	Blood urea nitrogen	−0.67
MGV	00–15	Glucose	−0.75
MGV		Chloride	0.66
MGV		ALT	0.69
SG	00–27	Creatinine	0.71
MGM	00–17	AST	0.71
MGM		Triglycerides	−0.76
MGM		Cholesterol	−0.76
Ian	00–70	Lactic dehydrogenase	−0.87
Ian		Albumin	−0.69
LDDM	03–93	Creatine phosphokinase	0.70
LPMR	10–97	Creatine phosphokinase	0.85
LPLC	10–99	Chloride	0.70
SubG	00–60	Lactic dehydrogenase	0.71
SubG		Triglycerides	−0.67
SubG		Albumin	0.77

[a] See footnote 1 for list of abbreviations.

Table 6
Criterion correlations (ρ) between the proportion of damage within brain structures and blood measures in rats that were seized and administered ketamine about 1 year previously.

Structure		Measure	ρ
AHIPM[a]	10–70	Potassium	−0.67
LAVL	05–50	Alkaline phosphatase	0.80
SNc	10–40	Sodium	−0.69
SNc		Creatinine	−0.65
SNl	00–10	Phosphorus	0.72
CA3	00–45	Phosphorus	0.73
MDM	00–50	Potassium	−0.67
ASTR	00–20	Lactic dehydrogenase	0.73
DG	00–20	ALT	0.68
IBL	00–10	Uric acid	0.69
CA1	00–77	ALT	0.72
ENT	06–59	Albumin	−0.81
DSC	00–25	Albumin	−0.88
SubG	00–55	AST	0.65
SubG	00–55	Phosphorus	0.67
MGD	00–13	AST	−0.66
SG	00–05	Body weight	−0.67
LPLR	00–40	Phosphorus	0.67
CM	20–43	Thyroid-stimulating hormone	0.70
LDVL	00–17	Glucose	−0.77
LDVL		Uric acid	−0.67
LDVL		Cholesterol	−0.83
LDVL		Free thyroxine	0.81
LDVL		Albumin	0.80
LPLC	00–37	Alkaline phosphatase	0.67
DLG		Cholesterol	−0.70
VPM	00–45	Cholesterol	0.70

[a] See footnote 1 for list of abbreviations.

Table 7
Largest correlation coefficients (ρ) between proportion of damage within specific structures and wet tissues weights for seized rats injected with either acepromazine or ketamine 1 year after seizure onset.

Structure	Measure	ρ
Acepromazine		
LADL[a]	Thymus	−0.73
LADM	Thymus	−0.76
BVL	Thyroid	0.71
BMA	Thymus	−0.72
SNR	Thymus	−0.71
PVP	Thyroid	−0.66
EP	Brain	0.69
SubG	Adrenals	−0.68
VM	Thymus	−0.73
MGD	Thyroid	−0.67
MGV	Thyroid	−0.69
MGM	Thyroid	−0.75
PF	Brain	−0.80
Ketamine		
CL	Thymus	−0.68
DEN	Brain	−0.77
LADL	Brain	−0.78
BMP	Brain	−0.66
EP	Gonads	−0.65
LHBM	Thymus	−0.66
CPU	Pituitary	−0.65
LDVL	Thyroid	−0.70
DLG	Thyroid	−0.88
VLG	Thyroid	−0.75
GX	Pituitary	−0.75
PF	Brain	−0.70

[a] See footnote 1 for list of abbreviations.

3.9. Wire cage versus plastic home cage differences on blood and tissue measures

Except for brain weight, two-way analyses of variance for all of the blood measures and wet tissue measures as a function of treat-

Table 8
Means and SEM for body weights, blood measures, and single-organ weight difference for rats maintained in plastic versus wire cages for about 1 year after seizure induction.

Measure	Wire cages (n = 26)		Plastic cages (n = 28)	
	M	SEM	*M*	SEM
Body weight (g)	698.1	23.6	687.2	22.9
AST (U/L)	167.1	21.2	166.4	12.3
Glucose (mg/dL)[c]	9.7	0.3	11.9	0.5
Blood urea nitrogen (mg/dL)	8.5	0.4	8.2	0.5
Creatinine (mg/dL)[a]	9.3	5.5	21.8	2.6
Sodium (mEq/L)[c]	151.1	0.4	155.4	0.6
Potassium (mEq/L)[a]	7.1	0.2	7.8	0.2
Chloride (mEq/L)	105.0	0.5	106.4	0.6
Calcium (mg/dL)[b]	3.1	0.02	3.2	0.04
Phosphorus (mg/dL)[b]	2.3	0.1	2.8	0.1
Lactic dehydrogenase (U/L)[c]	584.7	43.6	194.9	48.2
Creatine phosphokinase × 10^{2}[b]	97.2	43.1	366.2	62.3
Alkaline phosphatase (U/L)	134.2	10.3	123.3	9.6
ALT (U/L)	93.1	11.2	88.0	7.8
Uric acid (mg/dL)[c]	112.0	9.5	205.1	19.1
Triglycerides (mg/dL)	4.7	0.7	5.4	0.8
Cholesterol (mg/dL)	5.2	0.6	6.3	0.6
Thyroid-stimulating hormone (mIU/L)[b]	0.020	0.004	0.008	0.002
Free thyroxine (pmol/L)[a]	20.9	1.3	17.4	1.0
Thyroid (mg)[b]	31.2	3.1	46.2	3.8

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

ment (acepromazine vs ketamine) and home cage condition (wire cages vs plastic cages) demonstrated no statistically significant interactions between cage condition and drug treatment. Post hoc analyses indicated the significant interaction [$F(2,37) = 6.42$, $P < 0.01$] was due to the lighter brain weights of normal rats maintained in the plastic cages compared with the wire cages and to the relatively heavier brain weights of ketamine-treated seized rats compared with normal rats that were maintained in the plastic cages. The means and SEM for all measures for rats that were maintained in wire cages versus plastic cages for the approximately 1 year after the induction of the seizures are listed in Table 8.

The rats maintained in plastic cages with bedding had significantly (all $df = 1, 43$) higher levels of glucose ($F = 12.30$, $P < 0.01$, $\omega'^2 = 20\%$), sodium ($F = 23.85$, $P < 0.001$, $\omega'^2 = 33\%$), calcium ($F = 10.39$, $P < 0.01$, $\omega'^2 = 16\%$), phosphorus ($F = 8.38$, $P < 0.01$), creatine phosphokinase ($F = 11.62$, $P < 0.01$; $\omega'^2 = 19\%$) uric acid ($F = 16.21$, $P < 0.01$, $\omega'^2 = 25\%$), but lower lactic dehydrogenase ($F = 33.56$, $P < 0.001$; $\omega'^2 = 40\%$), thyroid-stimulating hormone ($F = 7.95$, $P < 0.01$, $\omega'^2 = 14\%$) and free thyroxine ($F = 4.58$, $P < 0.05$) compared with those that had been maintained in wire cages. The rats maintained in the plastic cages also had heavier thyroid wet weights ($F = 9.20$, $P < 0.01$, $\omega'^2 = 18\%$). There were no significant cage differences with respect to the other tissue weights.

4. Discussion

A single injection of ketamine or acepromazine shortly after the display of SE resulted in remarkably different and quantitatively discriminable patterns of brain damage that was evident 1 year after seizure induction. The correlation between the proportions of neuronal dropout within 100 structures for rats that had been seized with lithium (3 mEq/kg) and pilocarpine (30 mg/kg) and then injected immediately after the onset of rearing and forelimb clonus (SE) with either acepromazine (25 mg/kg) or ketamine (100 mg/kg) was only 0.40 (16% shared variance). That the postseizure treatment produced greater discrepancy than the cholinergic concentrations that precipitated the SE is indicated by the much stronger correlation of 0.86 in damage scores in 199 structures between rats seized with lithium/pilocarpine and those seized with the traditional [30] 300 mg/kg pilocarpine [31].

Direct comparison between the two groups indicated that mean overall damage did not differ between ketamine-treated and acepromazine-treated rats. However, those seized rats treated with ketamine showed more damage within the limbic regions, whereas those treated with acepromazine showed more damage within the thalamus. The differences in damage in only four major areas were sufficient to accurately classify the postseizure treatment condition of 96% of the 28 seized rats. The presence of substantial albeit different patterns of damage appears to contradict the absence of damage following ketamine treatment by others [4,15]. However, these rats were often killed within 3 days of SE.

When more precise resolution of "the neuromatrix" was considered, the differential damage within the APIR, PRS, basolateral amygdaloid nucleus (ventral part), lateral posterior thalamic nucleus (laterorostral part), and medial geniculate (ventral part) completely discriminated the two groups of 28 rats. Because discriminant and multiple regression analyses do not include variables that explain the same source of variance, there are many other structures that could have completely discriminated the two groups, such as the nucleus reuniens, basomedial (posterior) amygdala, and centromedial thalamic nucleus. All of these structures [34–36] have been implicated in the evolution and pathways of cholinergic seizures and the correlative brain damage.

The most obvious behavioral consequence of injecting acepromazine versus ketamine following SE is the absence of the emergence of spontaneous seizures after the classic "silent period." Although the consequences of ketamine may have terminated the reactive neurogenesis that has been postulated to contribute strongly to the aberrant synaptic reorganization promoting these seizures [37], the differential damage in the greater damage within the APIR may have also prevented kindling. The piriform cortices have been long considered the source of electrical kindling [38]. Clearly, the emergence of spontaneous seizures in the two groups following induction of SE with lithium/pilocarpine was not related to the amount of damage but rather the *pattern* of neuronal dropout. Photomicrographs of the histomorphological anomalies were similar to those published previously [2,3,5] and hence are not reproduced here.

The marked difference in the mosaic of damage between the two groups required separate correlational analyses for the two groups between measures of brain damage, wet tissue weights, and blood measures. The multiple correlations between the various damaged structures and blood measures contain a potential wealth of information, given the strength of the associations and the statistical criterion employed for their selection that may ultimately reveal the complex dynamics between the neuromatrix and organ function. However, only the most conspicuous features are discussed here.

The first most obvious mosaic difference was reflected in the opposite direction of the strong correlations between TSH and the amount of damage within the thalamus for the seized rats treated with acepromazine versus ketamine. The differential effect of the postseizure treatment on thyroid function was noted with the correlations of thyroidal measures and specific brain structures as well as thyroidal morphology. The acepromazine-treated rats had smaller follicles compared with the ketamine-treated or control rats. Dopamine agonist-mediated inhibition of acetylcholine release, the major seizure-precipitating neurotransmitter in this model, is strongly modified by thyroid hormone status [39]. The effects of differential agonism or antagonism of dopamine receptor subtypes on seizure promotion is clear [40,41].

Second, damage within the inner blade of the dentate gyrus, proximal to the areas of neurogenesis [37], was associated with elevated sodium, triglycerides, and cholesterol but diminished thyroxine and lactic dehydrogenase. Considering the reduced pancreatic weights displayed by these rats, this pattern would also be congruent with the observation by Sarrat [25] who demonstrated that small lesions within the granule cells of the hippocampus disrupted functioning of pancreatic islet beta cells and vice versa. The elevations in AST and ALT of the acepromazine-treated rats, compared with seized + ketamine or normal rats, are compatible with pancreatitis.

The elevation of these two enzymes is also suggestive of renal dysfunction. The general pattern is consistent with anomalies within the kidney–thyroid system [42] which involves varied patterns of water and electrolyte anomalies such as water retention and diuresis. Only the acepromazine-treated seized rats displayed a strong (and positive) correlation between time since seizure induction and elevation of electrolytes and other enzymes frequently coupled to alterations in kidney function. The kidneys of about 10 to 20% of these rats are often discolored (yellowish) and are reduced in size and shape (oval rather than elliptical).

Third, these results demonstrated that seizure-induced damage has long-term effects on the pathology of organs and would certainly have relevance within clinical settings. Hypoxia, systemic lactic acidosis, hyperkalemia, CO_2 narcosis, acute renal tubular necrosis, hyperpyrexia, aspiration pneumonia, blood leukocytosis, and pleocytosis of the cerebral spinal fluid are common and potentially serious immediate complications of SE [43]. Seizure-induced damage affects every organ. For example, Boyko [44] found that injections of 2 to 4 nmol of kainic acid into the thalamus and correlative cell loss, particularly within the ventral, dorsomedial, lateral, and reticular nuclei, resulted in the appearance of necrotic cells around the intramyocardial arterioles and venules within the midventricular myocardium within about 3 days. There was also loss of cells in CA3 and CA4 in the hippocampus.

Gross lesioning of the cerebral cortices in mice affected thymus and spleen weights, but not liver or body weights [26]. Lesions within the left cerebral cortices reduced spleen and thymus weights compared with controls, whereas lesions within the right cortices increased these weights. The reduction in spleen weight for left hemisphere lesions was about 11%, whereas the increase in thymus weight following right hemispheric lesions was about 20%.

The immunocompetence of antibody-secreting spleen cells was decreased by left but increased by right hemispheric lesions. In our study, the spleens of the acepromazine-treated seized rats were 28% lighter than those of controls, whereas thymuses of the ketamine-treated rats were 72% heavier than those of controls.

Limbic seizures are usually considered within a pejorative context. The results of the present study suggest there may be *positive* consequences of postseizure treatments. The ketamine-treated seized rats had heavier thymuses than either the acepromazine-treated seized or control rats. Typically the thymus involutes with age. The body weights of ketamine-treated rats were also greater than those of either group. We [45] have found the fat is morphologically different. In addition, these rats display behaviors more typical of younger adult rats, including a lower incidence of spontaneous tumors. This increased weight is specific to males. Female rats seized and given ketamine do not gain weight compared with controls, whereas female rats seized and given acepromazine become obese [46].

Considering the practical importance and political influence from federal agencies concerning housing conditions, particularly for long-term studies, the multiple differences in blood measures and differences in thyroid weights between rats housed in the now preferred plastic shoebox cages and those housed in traditional wire (steel) cages are significant. The increased glucose and creatine phosphokinase levels, reduced thyroid-stimulating hormone and free thyroxine levels, and increased wet thyroid weights only for rats maintained in plastic cages would suggest less ambulation and perhaps low-level goiter. Such caging effects are not new and are similar to those reported 30 years ago [47].

Considering the strength of these housing effects compared with postseizure treatments on commonly employed measures, housing conditions may be important to consider when designing long-term studies involving permanent changes [48] such as upregulation of T-type calcium channels [49] in epileptic rats. Su et al. [45] found that 54% of CA1 pyramidal cells, which normally fire in a regular mode, converted to a burst-firing mode. T-type Ca^{2+} channels are also abnormally expressed in cancerous cells [50]. Only a small depolarization of the cell membrane, within the range potentially affected by changes in blood chemistry, is required to open these channels.

The increased levels of glucose and creatine phosphokinase, but reduced levels of thyroid-stimulating hormone and free thyroxine, in conjunction with the increased thyroid weights for rats maintained in the plastic cages but not wire cages may be specific to older rats. In a previous study [47], these variables did not differ between rats maintained in similar plastic and wire cages. We suggest the inclusion of tissue weights, blood measures, and metabolic indices in future studies so that the quantitative values for these variables (and hence the "state of the organism") from environmental conditions such as caging can be compared and accommodated.

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